FINAL REPORT OF WORKSHOP CONFERENCE ON

SPACE RADIATION BIOLOGY

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SPACE RADIATION BIOLOGY

The Division of Biotechnology and Human Research of the Office of Advanced Research and Technology, National Aeronautics and Space Administration, sponsored this Workshop Conference on Space Radiation Biology at the Donner Laboratory, Medical Physics Division of the University of California, Berkeley, September 7-10, 1965, under the chairmanship of C.A. Tobias. Local arrangements were made by Ronn Patterson, of U. C. Extension Division, Igor Blake of the U. C. Donner Laboratory Business Office, and a committee of local scientists consisting of Philip Schambra, Henry Aceto, and John Lyman. There were about 150 scientists present, including representatives from several countries. The discoveries of the Van Allen belt and of solar flares, as well as the presence of external ultraviolet radiation in extraterrestrial space, are providing new challenges in radiation biology. The questions posed ranged from the problem of the origin of organic molecules in radiation fields to the safety of man in space missions of long duration. Most of the space radiation spectrum can now be reproduced by high-energy accelerators, but experimental studies with the heavy particles are of relatively recent origin.

In his introductory remarks, Walton Jones of NASA emphasized that further knowledge in heavy-ion radiation biology must be forthcoming before long-term exploration of the planets and the moon can be considered safe.

RADIOLOGICAL PHYSICS

Chairman: Ernest C. Pollard
Pennsylvania State University

In the first paper, presented by B. Larsson, University of Uppsala, the physical characteristics of protons in the 50 to 400 MeV range were discussed. Most of his presentation centered around the 185 MeV proton beam, with which he has worked for a number of years. This energy is typical of protons found in solar particle events. The predominant means of energy loss of such protons is by the ionization process; the contribution from nuclear reactions is small, and one is able to predict with accuracy the dose at various depths within tissue. The role of induced radioactivity, particularly Carbon-11 activity, and its production after whole-body irradiation are presently being studied in Sweden.

F. Cowan of Brookhaven reviewed the manner in which high-energy particles in the GeV range lose their energy in matter. Secondary particles produced by nuclear interaction in this energy region are especially important since they decay into other members of the same group with reduced energy. The long mean-free path for the production of these particles makes dosimetry at such high energy difficult. Thus, the dose and applicable quality factor or RBE at a point are strongly dependent not only on the identity of the primary particles but also on the geometric factors which determine the amount of material the particles have previously encountered. Fortunately, the flux of these high-energy particles is low relative to that of the lower-energy particles previously discussed.

The "thermal-spike" model of radiation interaction in various media was described by A. Norman, UCLA. The lifetime of such spikes is long enough for chemical reactions to take place, especially if the process is nearly spontaneous at ambient temperature. The large pressures due to expanding material caused by the thermal spikes account for the explosive growth of vapor bubbles in liquids. Such vaporization complicates calculations of heat flow away from the spike. Enzyme inactivation data can, in some instances, be explained by assuming that the thermal spike of heavy ions raises the local temperature several hundred degrees. The major obstacles in establishing the validity of the thermal spike model in biological material is the lack of knowledge of the biological structures themselves.

The heavy-ion tracks made visible in certain crystals, however, does not seem to be explained by the thermal-spike model. According to R. Fleischer, G. E. Research Laboratory, the mechanism seems to be one of explosive positive-ion migration to interstitial sites where the damage can be amplified still further by the large forces between adjacent ions. A discrete threshold exists for the formation of such tracks. A meteorite has been found with such structure, and the tracks noted in it are believed to come from ions in the galactic cosmic rays heavier than iron.

The nuclear star produced at the end of the track of a negative pion produces several low-energy particles which have high LET and great efficiency for biological damage. J. Baarli of CERN, Geneva, reported results of studies on a 70-MeV pion beam obtained from the 600-MeV proton beam at the CERN cyclotron. The beam was contaminated with 30 percent muons and electrons. The dose rate on the beam axis at the Bragg peak was 2.2 times the dose rate at the beam entrance. The quality factor was found to be 2.7 at the top of the Bragg peak and 3.4 in the middle of the downward slope. An assumption of 20 MeV of local energy deposition per nuclear star added to the theoretical Bragg curve fits the experimental points well.

C. Richman, Graduate Research Center in Dallas, reported results of several biological experiments performed with a 90-MeV pion beam from the Berkeley 184-inch cyclotron. A contamination of 40 percent muons and electrons was reported. The ratio of dose in the Bragg peak to the plateau region was measured to be roughly 1.6. The effect of the peak is clearly seen in the biological experiments. The reduction of growth rate of Vicia faba, the number of anaphase abnormalities in the cell chromosomes and percentage of cells having micronuclei were all considerably greater in the Bragg peak-irradiated samples than in the plateau-irradiated samples. The peak-to-plateau ratio of anaphase abnormalities ranged from 2.2 to 2.6 in the experiments utilizing different dose rates. Preliminary results of viability studies on ascites tumor cells in mice show the same behavior.

Newer dosimetry methods were described by M. Raju, (UC, Donner); he utilizes lithium drifted silicon detectors in measuring energy loss and total energy of protons and alpha particles at various energies. Measured values agreed well with calculated values. At the Bragg peak, the energy distribution of particles peaked at about 10 percent of the incident particle energy for both 40-MeV protons and 910-MeV alpha particles. This means that the mean LET at the Bragg peaks is relatively low; i.e., 8.3 keV per μ and 10 keV per μ, respectively.

A. Koehler of Harvard discussed the application of very small (0.5 mm by 0.5 mm by 0.1 mm) silicon diodes in determining depth dose distribution in water phantoms. Such diodes, when preexposed to 2×10^6 rad, showed a 1 percent change in sensitivity after a further exposure to 10^5 rad. This is stable enough to make frequent calibrations unnecessary. Energy dependence of the sensitivity was measured in stopping a proton beam using a nitrogen ion chamber as a reference. An interesting and not fully understood discrepancy between the measured and expected ratio showed up at the end of the proton range. The discrepancy is thought to be caused by scattering of low-energy particles out of the ion chamber. By turning the detector on edge, a spatial resolution of 0.1 mm can be obtained.

N. Baily, UCLA, pointed out the problems encountered in trying to develop a truly tissue-equivalent dosimeter. No single material is tissue-equivalent with all the necessary characteristics over the entire range of particle energies. Thus, the best compromise must be found for the particular application desired. The two types of dosimetry considered were macrodosimetry, in which the average dose over a relatively large volume and a large number of events is measured, and microdosimetry, in which the energy deposition per event is measured in small biologically significant volumes such as cell nuclei or chromosomes. Various problems, such as wide angular scatter of a particle beam and dose buildup from a high-energy monoenergetic particle beam, make the design of a tissue-equivalent chamber for microdosimetric studies difficult. Several such chambers and detectors were described in which an attempt was made to minimize the various difficulties.

The final paper in this session by N. Oda, Tokyo Institute of Technology and UC, Berkeley, described different approaches for the dose correction of the contribution of delta rays produced by heavy ions. When the velocities of the primary ions were equal, the low-energy electron yield was proportional to the total LET; when the velocities were different, the yield for higher velocity was greater than that for low velocity. Specific fluorescence was noted to be a function of total LET and ion velocity in the same way as are the yields for low-energy electrons. There may well be a fundamental interrelation between the specific fluorescence and the low-energy electron flux. Since the specific fluorescence can be considered similar to a biological inactivation cross section, it may be that low-energy electrons play an important role in biological inactivation.

HEAVY ION EFFECTS ON MAMMALIAN SYSTEMS

Chairman: Arthur C. Upton, ORNL

The initial paper, presented by A. Searle of Harwell, dealt with the differences observed between neutrons and gamma rays in producing genetic mutations in mice. Compared to Co^{60} gamma rays, the RBE of fast neutrons was shown to be about 20 for dominant visible mutations and 6 for specific locus mutations. Dose rate effect was also observed; genetic mutation was greater in mice which had been exposed to chronic doses of both low-LET and high-LET radiation than to acute doses.

The paper by L. Cole of the U.S. Naval Radiological Defense Laboratory, San Francisco, showed a high carcinogenic effect of fast neutrons. In mice exposed to sublethal doses, the RBE of fast neutrons was reported to be about 2 or 3 for producing tumors of the gastrointestinal tract. Increased incidence of kidney and liver tumors was observed in neutron-irradiated animals which had been stressed with carbon tetrachloride to increase the rate of cell turnover. This carcinogenic effect of high-LET radiation appears to be associated with its mutagenic action, for chronic exposure to fast neutrons increases the incidence of both cancer and genetic mutation.

High-energy protons and alpha particles are similar to 250 kVp X-rays in producing dominant lethal mutations. These experiments were described by J. Ashikawa of USC and LLU. The effects on the testes of mice were also similar to those of X-ray. Mice which had been irradiated with whole body doses of 25 to 30 percent lethality in 30 days showed an initial fertile period followed by sterility for about a month. These results are not surprising since the LET value of 730 MeV protons and 910 MeV alpha particles are in the same range as 250 kVp X-rays. Gut death predominates in particle-irradiated animals while X-irradiated animals show a predominantly haematopoietic death. The differences seen in the relative predominance of gut and marrow death are probably due to differences in the microscopic dose distribution in bone marrow cavities and in soft tissues. Fractionating the dose will attenuate the gut death. A maximum early recovery was noted in animals which had received two proton doses separated by an interval of 3 hours. The RBE of high-energy protons and alpha particles depends both on the dose and on the time after irradiation when mortality is evaluated. Based on an LD50 dose and compared to 250 kVp X-rays, the RBE varies from 0.96 for 730 MeV protons and 0.90 for 910 MeV alpha particles at 6 days to 0.75 and 0.73, respectively, at 30 days post irradiation.

Studies of the effect of whole-body proton irradiation of Macaca mulatta were reported by I. Lindsay. The range of 32 MeV protons is only 1 centimeter in tissues so that the gastrointestinal and haematopoietic tissues are spared. All animals, however, exposed to doses greater than 6700 rads had died by the fourth day, presumably of CNS involvement. With the 32 MeV energy, no death was observed from the 4th to the 20th day post irradiation. At lower doses this energy of proton produced marked cutaneous damage with ulceration of the skin accompanied by secondary infection. With proton energies higher than 55 MeV, both gastrointestinal and haematopoietic syndromes were observed. Generally the gastrointestinal and haemorrhagic symptoms were more severe than observed with an equivalent dose of X-rays.

W. Haymaker, from Ames Research Center, NASA, reported on the findings in the brains of these monkeys. Marked inflammatory reactions were observed 1 to 6 days post irradiation. The accumulation of glycogen, particularly in white matter and in glial cells, was observed in animals sacrificed for 6 days post irradiation.

S. Taketa, Ames, NASA, presented the changes in erythrocyte and leucocyte blood counts in monkeys exposed to whole-body doses of high-energy protons. The results were generally similar to those observed in Co^{60} gamma radiation.

When both the anterior and posterior portions of the lens of the mouse are carefully examined for opacity, neutron doses as low as 5 to 6 rads were found to produce some opacification. The corresponding dose of 250 kVp X-rays required to produce such opacification was 60 rads. At low doses a dose fractionation effect was not seen. These results were presented by J. Bateman of Brookhaven.

The effect of very heavy ionizing particles with masses greater than iron in cosmic rays was analyzed by H. Curtis of Brookhaven. He has used a deuteron microbeam to simulate the densely ionizing track of a cosmic ray particle. Doses of 200,000 rads were required to produce visible damage to nerve cells. From his studies, he concluded that the high radio-resistance of the nerve cells would make destruction of neurons by cosmic rays insignificant in comparison to loss of the cells by natural death.

SPACE RADIATION HAZARDS TO MAN

Chairman: H. D. Bruner, AEC

The physical nature of space radiation was described by two speakers in this session. The first of these, S. B. Curtis of Boeing, Seattle, explained the magnetic rigidity of space radiation as originally proposed by P. S. Frier and W. R. Webber in 1963. Curtis pointed out that with greater shielding the skin dose is markedly reduced, but the dose to deeper structures is little affected since body self-shielding has already stopped most of the less energetic particles. The other speaker on this topic was W. H. Sweet, Harvard, who pointed out that there is a 10- to 20-minute delay between the appearance of a visible solar flare and the arrival of particles in the region of the earth. There is an increase in intensity of the radiation for a day or two and then a decline to preflare intensity in about 5 days. The flux of high-energy particles reaches a maximum earlier than the flux of low-energy particles. Generally about 10 percent of the flux is alpha particles--the balance being protons, most of which are in the 10 to 100 MeV range.

The paper presented by J. Brennan attempted to define the parameters which determine the effective residual dose (ERD) of radiation. The sources of information for evaluating the various parameters were mentioned and were given as follows:

1. Radiation accidents
2. Atomic bomb casualties
3. Exposures in weapons testing
4. Conventional radiotherapy
5. Special types of radiotherapy, such as particle-beam
6. Animal experiments and fundamental radiobiology
7. Space radiobiology

An equation was given which attempted to relate all the parameters to the effective residual dose. The resulting factor had a fairly wide range which could be reduced if the parameters were more precisely known.

Therapeutic pituitary irradiation with an alpha-particle beam was briefly discussed by J. H. Lawrence of the UC Donner Laboratory. Some of the delayed effects of this radiation on brain tissue at 2000 to 3000 rad dose level were mentioned. A motion picture was presented showing the technique and results of particle-beam irradiation for acromegaly.

The data available from radiation accidents were presented by Gould Andrews, ORNL. The advantage of these cases for study is that the individuals are almost always normal prior to radiation, and they are thoroughly studied following radiation. The disadvantage is that the dose rate is usually high and the dosimetry is poor. The typical haematological response to acute whole-body radiation was reviewed, and the quantitative variations with varying dose were mentioned. The potential role of plastic film isolators for patients who received doses which would be expected to cause a haematologic syndrome was mentioned as a very promising means of reducing infection. Marrow grafts would be restored to in the more severely irradiated cases. The single accident which has contributed to the knowledge of the effect of radiation for weeks at fairly high doses was discussed. This was the accident involving a Mexican family which had a Co^{60} source about their household for over 100 days. These cases were remarkable in that they failed to show evidence of recovery of the haematological picture at 6 weeks. Minimum-to-maximum dose estimates of two cases cited ranged from between 984 to 1717 rem in 106 days to between 1818 and 2897 rem in 96 days. The possibility of using radioprotective drugs for radiation exposure in space was mentioned.

In a review of records of 93 cancer patients who received whole-body gamma radiation and of the records of 7 nuclear-radiation-accident victims who were all treated at ORINS, C. C. Lushbaugh, ORNL, showed the extent to which symptoms of the prodromal radiation syndrome can be related to the radiation dose. Since the prodromal syndrome occurs 2 to 6 hours following radiation exposure, it would be a threat to the performance of the astronaut. By statistical analysis of the data, the effective dose in producing symptoms in 50 percent of the cases were as follows: anorexia, 68 rad; nausea, 104 rad; vomiting, 137 rad; fatigue, 97 rad; diarrhea, 183 rad; and death, 316 rad. The goodness-of-fit was borderline acceptable for diarrhea using the log dose transformation and either borderline or poor for fatigue using the arithmetic dose or log dose transformation, respectively.

In a review of his experience with radiation in cancer therapy, E. L. Saenger of the Cincinnati General Hospital pointed out that the effect of half-body irradiation was similar to that of whole-body irradiation in producing nausea and vomiting. No nausea and vomiting was observed with doses less than 100 rad. More nausea and vomiting developed in his cases when the patient had received cancer chemotherapy.

As the chairman of this session, H. D. Bruner, had pointed out at the beginning that we have no direct information about the effects of whole-body exposure of man to particle radiation. Such information will probably not be available until after man has been exposed to significant amounts of such radiation in space. The information presented in this session has added insight as to what might be expected when such exposure occurs and what might be done to reduce the effect of such exposure.

MOLECULAR EFFECTS

Chairman: Leroy Augenstein
Michigan State University

The chairman remarked that although we are well past the dawn of the Atomic Age, it is still not possible to specify which initial events are of the greatest significance in producing the observed biological effect.

Horst Jung, Institut fur Strahlenbiologie, Karlsruhe, Germany, noted that for low energy protons and neutrons, collisions with the nuclei of the irradiated sample were the chief means by which energy was deposited. While less than 1 percent of the energy deposited by a fast particle is laid down by nuclear collision, upwards of 98 percent of the energy of epithermal neutrons is deposited in this fashion. It is felt that the alteration in the chemical composition of the biological target molecule could lead to permanent damage. The loss of enzymatic activity in an RNA-ase test system was found to be produced solely by the mechanism of nuclear collision.

It is known that ionization and electronic excitation are the major mechanisms of energy depositions for many types and energies of radiation. The role of these two processes in the production of trapped free radicals in biological macromolecules irradiated in the dry state was extensively discussed by Thormod Henriksen and Harold Steen, both of Norway's Norsk Hydro Institute for Cancer Research, and by K. Stratton, Harvard. Both the type and yield of "secondary" free radicals obtained from irradiations with particles of widely different LET were described by Henriksen. Ionizing radiations produce sulfur radicals and a doublet-radical from the protein backbone in enzymes. A third type of radical was observed if the enzyme was irradiated at 77° K and the radicals were then measured at room temperature at low microwave power. This unknown radical disappears much more rapidly than either of the other radicals, which may explain why it was previously undetected. Sulfur radicals were not observed below about 250° K for X or γ-rays, electrons, protons, or fast stripped nuclei from helium up as far as argon. However, Stratton reported that 300 keV neutrons produced a sulfur spectrum at 77^{o} K. It was found that as the irradiation temperature was increased, the yield of radicals increased. This increased yield, as a function of temperature, was found to be greater the lower the stopping power of the radiation. The deposition of energy by the electronic excitation can produce localized excitation or a free radical through charge separation. Leroy Augenstine, observed that up to 50 percent of the biological damage produced by X-rays may in fact be due to nonionizing excitations caused by the X-ray produced secondary electrons. H. Steen reported in his studies of UV-inactivation of dry trypsin that above 3000 Å there appeared to be little or no correlation between the measured yield of secondary radicals and the enzyme inactivation yield. However, in the wavelength region below 3000 Å he was unable to exclude the possibility that radicals played a major role in the production of enzyme inactivation. All the investigators agreed that the events subsequent to the initial energy deposition included interactions between excited states as well as energy transfer from the site of deposition to another site not originally affected by the irradiation. These events were illustrated by the appearance of the sulfur radical when samples of enzyme subjected to ionizing radiation at 77^{o} K were warmed to room temperature as reported by Henriksen. Further evidence for such energy transfer was given by Ronald Rahn, Bell Telephone Laboratories, Murray Hill, New Jersey, who described energy transfer in UV-irradiated DNA to the adenine-thymine pair and the subsequent transfer of the proton from the N_1 atom of thymine to the adenine to give an A^+T^- pair. This model is based upon the knowledge that thymine phosphoresces only upon losing the N_1 proton and the observed emission from UV-irradiated DNA has been shown to come from the thymine moiety.

After the interaction of radiation with the macromolecular biological target, followed by subsequent energy transfer and interaction between excited states, the significant biological event results. This event is probably a chemical change, and W. Szybalski, University of Wisconsin, believes that, at least in the case of cellular DNA, it may be modified by the operation of a repair mechanism. A model for this repair mechanism would include cutting the affected strand on both sides of the modified area, resynthesis of replacement parts for the excised area, and, finally, a closing of the 5'P to 3'OH link to complete the strand. Further work to improve this model is needed since it would predict that double strand breaks would be largely irreparable due to the resultant loss or erasure of information but diploid yeast are able to repair double strand breaks caused by heavy ions.

In the final analysis it must be admitted that this thoroughly stimulating session was not able to show whether ionization, excitation, or the free radicals formed by these processes constitute the significant event leading to the biological effect. While there appears to be a good correlation between yield of secondary radicals formed by irradiation of enzymes with ionizing radiation and the inactivation yield, a similar correlation was not found between UV-induced radicals and inactivated enzyme molecules. These divergent results point up the need for further work in this area to show what role (if any) free radicals play in radiation-induced biological damage. Work at liquid helium temperatures (now in progress at Donner Laboratory) should allow characterization of the initial radical centers; subsequent stepwise warming should then reveal the sequence of events leading to the secondary radicals. Attempts to correlate radical yield or radical disappearance with inactivation should be made at each step along this path. Only then can the role of the radical be specified as either a cause of damage or simply an indication of it.

EVALUATION OF COMBINED EFFECTS

Chairman: Douglas Grahn
Argonne National Laboratory

Most experimental studies have either involved radiation or some other single stress of the space environment. In this session pertinent studies relating to stresses other than radiation and their possible relationship to radiation were described. The effects of rapid transverse acceleration on the cardiopulmonary system were described by C. Nolan of the Mayo Clinic. One of the more critical areas in this system is the potential space between the anterior chest wall and heart. At an acceleration of 5 g, the pressure exceeds the osmotic pressure, and pulmonary edema results if the acceleration is long maintained. The relationship of the effects of this stress to radiation have apparently not been studied.

A mathematical model to help deal with the nonuniform exposure which is encountered with space radiation was presented by V. P. Bond of Brookhaven. In this model the stem cell survival is taken as the critical factor which determines the survival of the individual. If one can calculate the total number of stem cells surviving after exposure, one can predict whether the individual will survive or die. This model is potentially useful for evaluating effectiveness of any radiation with any distribution of dose, provided that (1) one knows which cells are of interest with respect to the biological factor in which one is interested; (2) the spatial distribution of these cells of interest; and (3) the dose effect relationship for the biological effect upon these cells.

Studies designed to evaluate the effect of the current Gemini atmosphere with respect to the problem of oxygen sensitization to radiation were presented by E. Roth, Lovelace Foundation. One such study has shown a slight increase in the sensitivity of mice to 250 kVp X-rays while another showed no difference. The disagreements point up the need for further work in this area.

In a study of chronic irradiation of 22 to 170 rad of protons over a 10-day period, J. Burke of Harvard has shown an increase in the size of lesions produced by injection of nonresident bacteria into the skin of the animal. Thus, even at these low dose levels, chronic irradiation may present a problem of bacterial infection.

Three papers dealt with the effect of radiation upon the functional state of the nervous system. The first of these was by R. Schoenbrun, UCLA, who showed electroencephalographic changes in the experimental animal with radiation doses of 500 rad delivered bilaterally to each hippocampus. The next paper was that of J. Garcia, Harvard, who has shown arousal of animals with doses as low as 10 mr. He has used this radiation as a signal in conditioning experiments. Surgical excision of the olfactory bulbs leads to a loss of this radiosensitivity, and the animals no longer sense such low doses of radiation. What the implications of this might be for the space traveler are uncertain, but possibly such radiation would lead to unusual personality manifestations during prolonged space flight.

Preliminary observations presented by L. W. McDonald, UC Donner Laboratory, of the post-rotational nystagmus in rabbits following 910 MeV alpha-particle irradiation of 500 rad suggest that after a period of no stimulation following irradiation, the nystagmus is markedly diminished or absent entirely. Such a loss of vestibular function might then cause aggravation of motion sickness which may already be present due to other stresses. Further study in this area is needed.

CELLULAR EFFECTS

Chairman: E. L. Powers
Argonne National Laboratory

Results of studies utilizing cultured mammalian cells were presented by L. Skarsgard, Yale, and by P. Todd, UC Donner Laboratory. Heavy ions were used in the studies presented by both speakers. The appearance of abnormal metaphases and chromatid exchanges were noted. The dependence of the RBE upon the LET for the two types of chromosome abberations was similar to the results obtained for cell survival. The high LET radiations show a linear increase of effect with dose, whereas the lower LET radiations show the so-called "two-hit response". F. de Serres, ORNL, and also S. Nakai, National Institute of Genetics, Japan, and R. Mortimer, UC Donner Laboratory, presented findings showing spectra of mutations with high LET radiations different from those observed with low LET radiations. The effects with the low LET radiations were dose dependent while with the high LET radiations they were less dose dependent. With densely ionizing high LET particles there are more gross chromosome deletions which increase linearly with the dose while with the lightly ionizing radiations the gross chromosome deletions require two-hit events and, therefore, increase with the square of the dose. Log survival curves of mammalian cells irradiated with low LET radiations are sigmoid in shape, while those with high LET radiations are exponential. This relationship was particularly brought out by P. Todd. A variety of environmental factors that alter the sensitivity of the reproductive capacity of cultured mammalian cells exposed to X- or gamma-rays fail to alter the sensitivity of cells exposed to densely ionizing radiations or alter them to a lesser degree. The effects of sublethal levels of sonic irradiations on yeast cells were presented by V. Burns, UC, Davis. It appeared that the metabolism of the cell was disturbed by some mechanism which made the cell membranes more permeable to small molecules. In this session, R. Haynes, UC Donner Laboratory, presented a review of experimental work showing the synergism between ultraviolet and more penetrating radiation. John Lyman, UC Donner, gave evidence that some of the damage produced by densely ionizing radiations in one biological system is reversible; namely, diploid yeast are just as capable of recovering from heavy ion irradiation as they are from X-irradiation.

SUMMARY

Attention was drawn to the widely different states of the art among the different disciplines discussed, from physics of the particles, to space radiation effect on man. It would appear that at the atomic, molecular and cellular levels quantitative data are at present available for a wide range of phenomena, relating radiation quality and quantity to the precise magnitude of the effects. On the other hand when multicellular organisms, and man are studied we find a large number of investigations but very few quantitative data that have sufficient reliability to serve as guidelines for protection of astronauts or as testing grounds for precise mechanisms. Yet it is in the realm of radiation effects on animals and man, where the practical needs are greatest: it is our aim to send man on prolonged space journeys including visits to the surface of planets. In order to accomplish this with safety and in fact to know eventually whether space radiations might represent a formidable barrier to man's exploration and colonization of space we must acquire quantitative information on the responses of man to the varied forms of space radiations, mainly based on the responses of animals. This general task will be difficult and time consuming to accomplish and there is not a complete agreement as to the best method to accomplish it.

On one hand, it is suggested to use the "large amount of X-rays and neutron data available" and on the other hand it is suggested to abandon the so-called "fundamental approach instead concentrating on testing animals closest to man in exposure situations most like those that might be encountered by astronauts". The former approach is thought inadequate by many, because the X-ray or neutron approaches leave out precisely the novel aspects of space radiations, namely the high LET particles. Even with X-rays or neutrons, data are deficient or missing when it comes to conditions most likely to be encountered on actual space missions: the simultaneous presence of a number of environmental stresses, superimposing on radiation, which in themselves can be near the limit of endurance. Many of the available data are thus not directly applicable to space flight.

The second approach, that of testing significant groups of animals in simulated space environment also has weaknesses. Because of the variability of the individual and because of the manifold symptoms and effects that can occur, one usually ends up with very large groups of animals to be exposed to a variety of radiation conditions with massive batteries of biological and biochemical tests. In the past one often encountered unexpected complicating factors in such experiments (e.g., epidemics), that seriously interfered with a reliable result. At the end, one is left with the necessity of converting the information by assessing its importance to man. Here we are still left with many unknowns. Sometimes new factors appear, due to progress in science which have not been included in the initial experiment. Each time such events occur, one must redesign the experiment, and start over again.

The third approach is to study basic biological effects with particles of similar properties as space radiations, at various levels of complexity, including molecular, cellular, and organismal effects and to establish meaningful and quantitative correlations, thus progressing from the understanding of the simpler to the more complex. Recommendations for permissible exposures follow the "current state of art". The current challenge is to find quantitative relationships between cellular and multicellular radiation effects. Some promising efforts have been made, e.g., V. Bond attempts to explain mammalian radiation lethality based on cellular effects in bone marrow. Still much remains to be explored about cellular and body control mechanisms. Mammalian and human data show such statistical variations because in addition to cellular effects homeostatic control mechanisms enter in, masking the effects of cellular damage until the control mechanism itself goes out of control.

Radiological Physics

Dr. Larsson's talk is indicative of the technical progress made in adopting protons for biomedical studies. Using the cyclotrons at

Uppsala, Harvard and Berkeley and the Berkeley heavy ion accelerator, it is now possible to simulate exposure of molecular and cellular systems to many of the heavy ions found in solar and cosmic rays. Also it is possible to simulate Van Allen Belt and solar flare spectra for studies with mammalian systems. We cannot as yet study the effects of uniform high LET radiation on mammals except near the very surface of the body. Further developments in heavy ion accelerators will be necessary before the biological effects of heavy ions can be explored fully. The interactions of high energy particles with matter is understood qualitatively. Much more work needs to be done in order to characterize the radiological physics of secondary particle spectra more fully. Biological effects depend on the primary energy exchange between tissue and particles. The distribution of delta rays should be known in much more detail and a good beginning is being made in this direction. Radiation measurement is undergoing revolution with the use of solid state detectors, which can give accurate local energy deposition measurements and also measure the LET spectra. Further developments are needed for simultaneous monitoring of an inhomogenous radiation field. These techniques, when applied to radiological physics of mixed radiations as those encountered in space, will make the biological studies more meaningful and help the complex monitoring problems in satellites. At the molecular level of radiation effects. we still have not completely solved the problem of what are the primary and the secondary interactions in biological macromolecules. It appears that primary interactions can be captured and measured only at very low temperatures, near those of liquid helium. The technique of such observations is being perfected at present. At warmer temperatures there is complex migration of excitation energy producing secondary radicals. Part of the radiation damage is annealed, part of it becomes irreversible macromolecular damage. Lethality appears to be correlated to irreversible alterations in DNA molecules, e.g. double strand breaks, and with other, sometimes very specific alterations, e.g. dimer formation. The detailed quantum mechanical steps that lead to the molecular damage would be most useful to know. Evidence was presented that biological material can in some instances recover from heavy ion damage, and one should know more about this. At the cellular level we have some excellent data now, particularly on mammalian cells on the quantitative aspect of the effects of high LET radiation. As L. Powers stated "radiation cellular biology is becoming important or significant and meaningful with respect to general mammalian radiation biology." For example cellular damage to bone marrow stem cells is accurately measurable and it leads to a prediction of hemopoietic lethality. A better comparison between cellular effects and physiological effects could add much to our present state of knowledge at the level of the whole animal. Powers also remarked that it is important to realize that the value of RBE (relative biological effectiveness) depends on the survival level and that there may be special significance of very high LET radiation, above 100-200 kev/micron. Repair of radiation damage at the level of nucleic acids is a very fundamental process that needs detailed study. Repair studies are only in their infancy for mammalian cell systems and for high LET radiation. Understanding of the nature of enzymic repair processes and perhaps their external humoral control could be of very great practical importance to space flight in addition to their basic importance to cell biology.

Synergism between radiation and other physical variables is of obvious interest to space flight, yet certain aspects of this have hardly been studied. Initial attempts are being made for understanding of possible synergism with weightlessness, vibrations, ultrasound, magnetic fields, temperature, etc. With ordinary radiations, most of the biological effects can be shown to be caused by ionizations and excitations. The role of thermal spike effects for heavy ions is not yet clear. Fleisher gave a convincing demonstration of thermal effects of fission recoils, which can burn micro holes into thin layers of matter. It is at the level of mammalian investigations, where much controversy still exists. By now we should have good quantitative data to predict the level and percentage of lethality, the levels of prodromal symptoms and the extent of late events in man. Yet with each study we realize the complexity and variability of biological material more and more. High energy protons have an RBE for lethality near unity. Yet proton effects differ in some important details from X-ray effects. The effects of low energy protons, alphas and of heavy ions, mixed with high energy protons have not as yet been studied. The intestinal radiation syndrome in mice and primates appears to be more important than hematological lethality. Burke has shown increased susceptibility in guinea pigs after protracted proton irradiation and it is striking that a high incidence of intestinal tumors was found after neutron irradiation and not after X rays. It has been suggested that the distinction between repairable and irreparable damage is lost when one deals with chronic effects. It is the depletion of cells that matters and the subsequent repopulation by normal cells. Repopulation depends more on the intrinsic properties of tissue than on the quality of the radiation injury. Howard Curtis challenged this point, citing evidence for cellular responses, e.g. chromosome effects, that are observable for a long time postirradiation and relate to life shortening effects as well as to the LET spectrum.

We need to establish more firmly three categories of information for radiations of various LET: (a) the relationship of repairable and irreparable cellular injury to radiobiological effects on the whole animal (b) the relationship of sublethal injury to radiobiological effects part of which might be repairable (c) the effects of radiations on tissue regeneration and repair. Quantitative studies on special organs and systems were cited at the conference as of direct importance to space flight. Some of these organs and systems include the lens and retina of the eye, the reproductive system which is very sensitive to high LET radiation, the vestibular organ, the adrenal cortex, skin, intestinal epithelium and bone marrow, including hemopoiesis, blood clotting and immunity mechanisms. It is anticipated that following exhaustive preparation on Earth, some effects may need testing in animals in space flight. Wright Langham discussed the role of man in space flight. He felt that in spite of the great concern over the radiation problems in space flights man is not fragile and that he can perform well under most conditions of space environmental radiation except when unusually large flares are present and he will be shielded against these. However we do need more information of the effects of medium dose levels on man: these became of concern for the first time with space exploration. We can give reasonable estimations for protection against acute lethal dose but prediction of dose levels where early unpleasant symptoms may occur is more difficult because of the great individual variation in sensitivity and the unknown effect of other environmental factors, particularly of weightlessness and vibrations. It is also desirable to know more in man about conditions for the occurrence of disorientation, anorexia, vertigo, vomiting and skin irritation. There are some delayed effects that may depend on conditions such as anemia, anoxia and fatigue at the time of irradiation. Hicks mentioned the need to know more about the psychological effects of prolonged exposures to moderate amounts of radiation. He felt that there is a possibility that small amounts of radiation might act in man, just as in animals an aversive reaction occurs as a result of irradiation. Radiation exposure might make the tasks that astronauts have to perform less pleasant and social relationships during space flight might also be aggravated. Levy called attention to the effects of prolonged stress on man. Several stresses in space might enhance adrenocortical output. Some studies on physiological stresses combined with radiation are called for. Hicks also wondered whether or not the injurious effects of radiation on blood vessels might be additive for protracted proton irradiation, and these might lead to anoxia-in nerve sheath tissue. Schonbrunn suggested that protracted exposure to radiation, particularly if combined with blood vessel injury and anoxia, might impair the osmotic balance in the brain and the delicate processes of learning and memory fixation.

Space environments do have different properties than the natural environments man has been accustomed to through the ages. No wonder that we must study the effects of these environments in detail and with diligence if we expect man to accommodate to them with a minimum of casualties and with optimum efficiency.

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